COUPLING REACTIONS AND SEPARATIONS IN PROPANE-ORGANIC-AQUEOUS TUNABLE SOLVENT SYSTEMS

A Thesis
Presented to
The Academic Faculty

By

Zainul Abideen Husain

In Partial Fulfillment
Of the Requirements for the Degree
Master of Science in Chemical & Biomolecular Engineering

Georgia Institute of Technology

August 2009

COUPLING REACTIONS AND SEPARATIONS IN PROPANE-ORGANIC-AQUEOUS TUNABLE SOLVENT SYSTEMS

Approved by:

Dr. Charles Eckert, Advisor
School of Chemical & Biomolecular Engineering
Georgia Institute of Technology

Dr. Charles Liotta, Co-Advisor
School of Chemistry & Biochemistry
Georgia Institute of Technology

Dr. Carson Meredith
School of Chemical & Biomolecular Engineering
Georgia Institute of Technology

Date Approved: 15th May 2009

– For my parents –
– who taught me that anything worth doing is worth doing well –

Acknowledgements

My foremost thanks go to my advisors, Dr. Charles Eckert and Dr. Charles Liotta. I have learned more these past two years than in any other period of my life. They have taught me to challenge ideas, be creative, and most of all to be confident. Their advice and support has enabled me to become an independent thinker and always question the significance and meaning of any project, experiment, or result. I would also like to recognize Dr. Carson Meredith for his support and advice as my committee member. A fresh perspective is essential for developing sound and meaningful ideas.

Special thanks go to the past and present members of the Eckert/Liotta group for their friendship, support, and amazing teamwork. Thank you to Megan Donaldson for training me. Thanks to the Sporcle, Kirpoxide, Fit-teh-moo and Bacteria crews as well as my office mates; you know who you are. Thank you also to Deborah Babykin for all of your administrative support. I would especially like to thank Vittoria Blasucci for being my mentor, close friend, and always having confidence in me.

Finally, I would like to thank my family. Without their support I would never have made it this far. Thank you to my parents for bringing me up with strong values and teaching me to be kind to everyone. Thank you to my brothers – all unique and extremely fun to be around.

Table of Contents

Acknowledgements iv

List of Tables vi

List of Figures vii

Summary viii

1 Introduction 1

2 Experimental 6

2.1 Materials 6

2.2 Experimental methods 6

3 Results and Discussion 9

3.1 Solvent Screening and Cloud Points 9

3.2 VLLE Water/Propane/Tetrahydrofuran 13

3.3 VLLE Water/Propane/Acetone 17

3.4 Optimal Propane-OATS System 19

4 Conclusions 21

5 Recommendations 22

5.1 Hydroformylation of p-Methylstyrene 22

5.2 Chiral Resolution of rac-1-Phenylethyl Acetate 24

5.3 Additional Solvent Systems and Conditions 25

References 28

List of Tables

Table 1 The observed conditions at which vapor-liquid-liquid equilibrium exists for water and an organic solvent under propane pressure. 10

Table 2 Hydrogen bonding, polarizability, polarity, and boiling points of screened solvents. 11

Table 3 Ternary phase behavior of the water(1) + propane(2) + tetrahydrofuran(3) system at 303K. 15

Table 4 Ternary phase behavior of the water(1) + propane(2) + tetrahydrofuran(3) system at 313K. 16

Table 5 Ternary phase behavior of the water(1) + propane(2) + acetone(3) system at 313K. 18

List of Figures

Figure 1 Schematic for homogeneously catalyzed reactions with heterogeneous separations and catalyst/solvent recycle using OATS process. 3

Figure 2 Jerguson sight gauge with ancillary equipment. 7

Figure 3 Sample loop modes and respective connections. 8

Figure 4 Phase transitions in propane OATS systems. 9

Figure 5 Ternary phase behavior of the water + propane + tetrahydrofuran system at T = 303 K. 15

Figure 6 Ternary phase behavior of the water + propane + tetrahydrofuran system at T = 313 K. 16

Figure 7 Ternary phase behavior of the water + propane + acetone system at T = 313 K. 18

Figure 8 Water content in the tetrahydrofuran-rich phase with increasing propane pressure at T = 303K. 20

Figure 9 Hydroformylation of p-methylstyrene in the presence of syn-gas 23

Figure 10 TPPMS (triphenylphosphine monosulfonate sodium salt) ligand 23

Figure 11 Chiral resolution of *rac*-1-phenylethyl acetate using *Candida antarctica* lipase B (CAL B) 25

Summary

Developing environmentally sustainable processes are essential to improving the quality of life for future generations. In addition to reducing our impact on the environment, we must design processes to be both economical and safe. A large component of any chemical process is the solvents used to dissolve the reactants and extract the products. The research presented here focuses on coupling efficient homogeneous reactions with simple heterogeneous separations using propane-organic-aqueous tunable solvent systems. Our tunable solvents undergo a phase separation upon application of propane pressure to a fully miscible mixture of water and an organic solvent. The propane based tunable systems detailed here eliminate carbonic acid formation and reduce product-phase contamination when compared with the equivalent CO_2 based solvent systems previously studied. Additionally, we eliminate the need to use buffers and thus solids handling equipment is not needed.

1 Introduction

Over the past decade, there has been a push toward sustainable separations due to environmental awareness and a desire to reduce operating costs. A sustainable technology is one that eliminates environmental impact through careful design. A significant component, often >50 wt%, of any chemical process is the solvent system used to dissolve the reactants and extract the products[1, 2]. Elimination or reduction of the amount of solvent used improves process economics and reduces environmental impact, hence making a more sustainable system. Several alternative solvents have emerged over the last 20 years to improve both reactions and separations including: supercritical fluids[3], gas-expanded liquids[4], nearcritical water[5], liquid polymers[6], ionic liquids[7], and perfluorinated molecules[8]. Several of the solvent systems mentioned fall into the category of tunable solvent systems. A tunable solvent is one which undergoes a change in properties upon application of an external stimulus, such as light, temperature, or pressure. Coupling fast reactions with simple separations are made possible through use of tunable solvent systems.

Chemical reactions designed for the pharmaceutical and fine chemical industries often require catalysts to ensure an efficient and cost-effective reaction. Homogeneously catalyzed reactions are advantageous because of greater catalyst activity and increased selectivity for the product of interest. Additional benefits include the elimination of mass transfer resistance across liquid phases and reduced product phase contamination. A significant disadvantage of homogeneous catalysis is the difficulty of both separating products, and recovering the often expensive catalyst from the solvent system. In

contrast, separation of both products and catalysts are made simple by employing heterogeneous catalysis; however, heterogeneously catalyzed reactions are often mass transfer limited. In order to improve the overall catalytic process, others have employed phase transfer catalysis, immobilized catalytic systems, tunable solvent systems, and switchable systems.

The organic aqueous tunable solvent (OATS) system examined here uses pressurized gas to switch a homogeneous water/organic solvent system into a heterogeneous one, coupling the advantages of both systems. A simple schematic for the OATS process is shown in Figure 1. Reactants enter the system and undergo a homogeneously catalyzed reaction. After the homogeneous reaction, the system is pressurized with a gas causing a liquid-liquid phase separation. The system is designed so that the catalyst remains in the polar water-rich phase and the product remains with the gas-expanded organic-rich phase. The water-rich phase is recycled back into the reaction vessel, ensuring minimal catalyst loss, while the organic-rich phase is easily decanted and sent for further product purification. After purification, the organic solvent can be recycled back into the process. The gas used to tune the system properties is filtered and recycled back into the process to cause the next phase separation. This process is fully sustainable where only reactants enter the system and only products leave. In addition, tunable solvents enable improved process economics by allowing for catalyst recycle, reduced solvent usage, and lower energy demand.

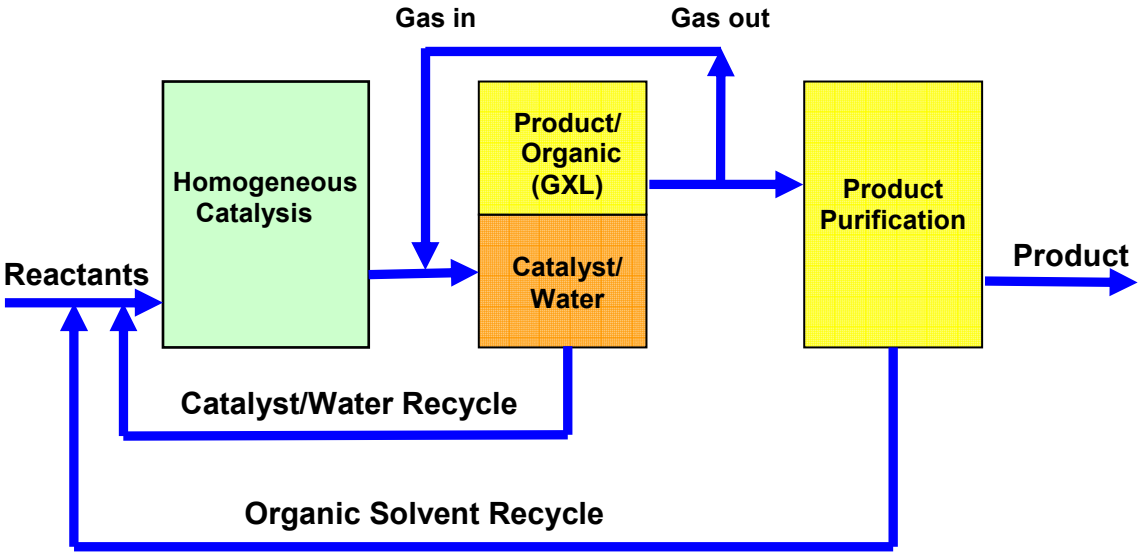


Figure 1 Schematic for homogeneously catalyzed reactions with heterogeneous separations and catalyst/solvent recycle using OATS process.

Our group has investigated CO_2 as a miscibility switch for various solvent systems consisting of organics with either water, polyethylene glycol (PEG), or perfluorinated molecules[9]. Donaldson et. al.[10] have studied the PEG-400/CO_2/1,4-dioxane system at 298K and 313K and the PEG-400/CO_2/acetonitrile system at 298K at pressures ranging from 5 to 8 MPa. Lazzaroni et. al.[11] examined the water/CO_2/tetrahydrofuran system at 298K, 313K, and 333K; the water/CO_2/acetonitrile system at 313K; and the water/CO_2/1,4-dioxane system at 313K at pressures ranging from 1 to 6 MPa. Additionally, Brenneke et. al. have investigated CO_2 as a switch with various imadozolium based ionic liquid/organic systems.

Upon pressurizing aqueous tunable solvent systems with CO_2, the water reacts reversibly with the CO_2 to form carbonic acid[12]. The formation of an *in-situ* acid is advantageous for acid catalyzed reactions, but prohibits reactions with an acid sensitive substrate, or where the catalyst is denatured by a low pH environment, such as enzymatic or base catalyzed

reactions. Broering et. al.[13] have tried to overcome this disadvantage by using common pH buffers; such as HEPES and phosphate based buffers. The addition of a buffer to the solvent system changes the liquid-liquid equilibrium due to the interactions between salts and solvents. Additionally, the buffer becomes ineffective at high CO_2 pressures due to reduced solubility of the buffer in solution. The salting out of the buffer from solution introduces the need for solids handling, adding to the complexity of the process.

The pH limitation is overcome by substituting CO_2 with a molecule that does not react with water, such as a low molecular weight hydrocarbon; eliminating *in-situ* acid formation. This allows for homogeneous enzymatic reactions, such as the kinetic resolution of phenyl ethyl acetate, or base catalyzed reactions, such as carbon-carbon coupling reactions, where a constant pH environment is desired; while still maintaining a heterogeneous separation. Cloud point and phase equilibria data are reported where ethylene or ethane pressure is used as a miscibility switch for aqueous systems with a range of common organic ketones, alcohols, amines, and esters at temperatures ranging from 283K to 333K and pressures up to 20 MPa [14, 15, 16]. A common limitation of both the hydrocarbon and CO_2 OATS systems is the need to pressurize to greater than 3.0 MPa to generate a phase separation, introducing the need for more specialized equipment.

We propose to replace CO_2, ethane, and ethylene with propane, a gas with a higher boiling point that is non-reactive with water and similar to low molecular weight hydrocarbons used in the past. To design the proposed OATS process effectively, the phase equilibria of the water/propane/organic system must be determined. Here we

explore the water/propane/tetrahydrofuran and water/propane/acetone systems at 303 and 313K and pressures ranging from 0.3 to 1.7 MPa. Composition data for each liquid phase are determined via the direct sampling method[17] and analyzed via Karl-Fischer titration for water content, gas chromatography-mass spectrometry (GC-MS) for organic content, and volume displacement for propane content. It is desirable to have minimal water in the organic-rich phase of our tunable solvent systems to limit catalyst loss and product phase contamination. High operating and capital costs are minimized by operating at as low a pressure as possible.

The water content in the tetrahydrofuran-rich phase is under 3 wt% at pressures >0.8 MPa in our optimal propane system, a big improvement when contrasted with a water content of 9 wt% at pressures >3.0 MPa in the equivalent CO_2 system[11]. This work is the first example of using propane pressure as a miscibility switch in tunable solvent systems.

2 Experimental

2.1 Materials

HPLC grade acetone (99.9%), acetonitrile (99.9%), dimethylformamide (99%), 1,4-dioxane (99%), 1-Methyl-2-Pyrrolidone (99%), tetrahydrofuran (99.9%), and water (99.9%) were obtained from Aldrich Chemical Co. and used as received. Instrument grade propane (99.5%) was obtained from Airgas and used as received.

2.2 Experimental methods

Phase equilibria for the water/propane/organic ternary system were determined by direct sampling[17] using a fixed volume Jerguson sight gauge (Figure 2). The direct sampling method compares well with the synthetic method described by Lazzaroni et. al.[18]. Prior to loading, the Jerguson cell was vacuumed (Fisher Scientific – Maxima C plus M4C) for 30 minutes to remove trace solvents and air. The Jerguson cell was loaded, using an air-tight syringe, with a weighed amount (Denver Instrument M-300, analytical balance ± 0.001 g) of water and organic through the injection port. A constant temperature air bath was maintained by a heater and fan system connected to a temperature controller (DiGi-Sense Temperature Controller – Model 68900-01). The temperature in the cell was monitored using a thermocouple (Omega type K) in contact with the bottom liquid phase. The thermocouple was calibrated against a platinum RTD (Omega PRP-4) with DP251 Precision RTD Benchtop Thermometer (DP251 Omega), providing an accuracy of ± 0.2K. The cell was allowed to reach temperature equilibrium for 2 hours before pressurizing the cell. Liquid propane at 80 bar was added from a piston pump (ISCO –

Model 260D Syringe Pump) slowly through a needle valve, while constantly shaking the cell until the desired pressure was reached. Pressure in the cell was measured using a Druck pressure transducer (PDCR 910) and read-out box (DPI 260) and were calibrated against a hydraulic piston pressure gauge (Ruska) to an uncertainty of ± 0.1 bar. The cell is mounted to a rotating shaft allowing the cell to be manually shaken. Once the desired pressure is sustained, the system is allowed to equilibrate for a minimum of 3 hours.

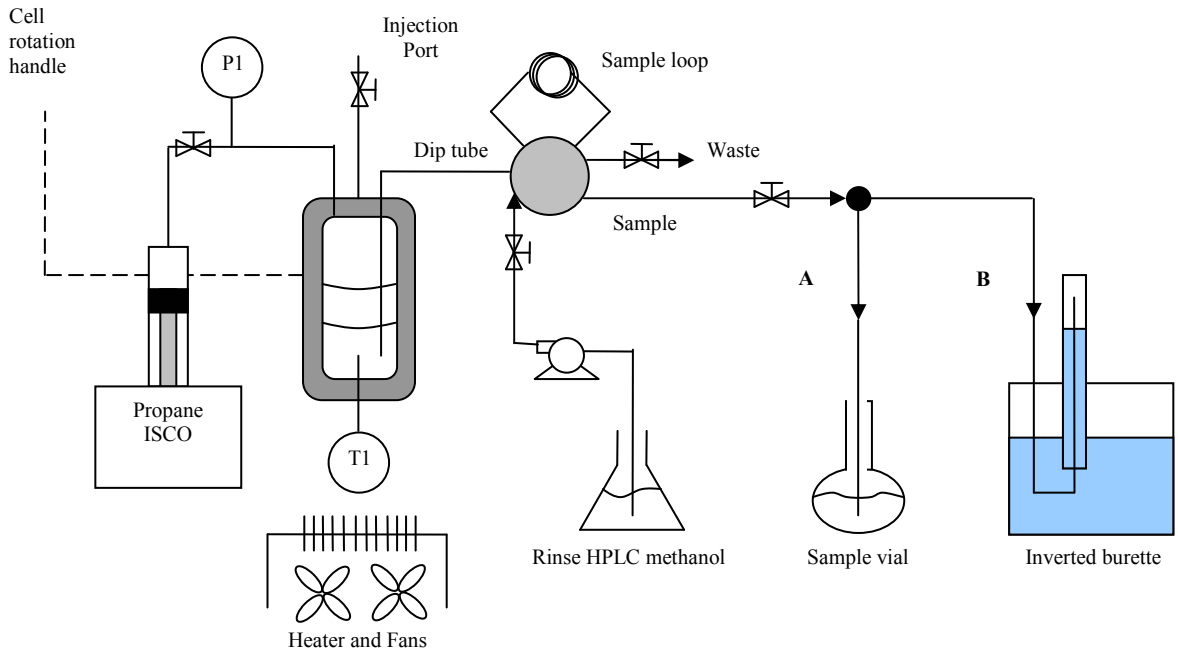


Figure 2 Jerguson sight gauge with ancillary equipment.

In the experimental diagram below; the dip tube, rinse solvent, sample line, sample loop, and waste line are interconnected to a 6-way valve. The valve has two settings, as shown in Figure 3. The 6-way valve is set to the 'fill loop' position. Opening the waste line, the sample loop is filled with a 0.5 mL sample from the bottom liquid phase, through the dip tube. The 6-way valve is then switched to the 'take sample' position. Line A or line B is connected to the sample line to allow for either water and organic analysis or propane

content. Samples from the cell were bubbled into and rinsed with HPLC grade methanol using an HPLC pump. These samples were analyzed for water content via Karl-Fischer titration (Metler Toledo – Karl-Fischer DL31). The organic content was measured via gas chromatography – mass spectrometry (Agilent GC-HP 6890 with a GCMS-HP 5973 and HP-5MS column) and quantified using a calibration curve ($R^2 = 0.995$). Propane content was determined by measuring the volume displaced while expanding samples through line B into the headspace of an inverted burette filled with water. The mass of propane was calculated from the displaced volume via the ideal gas equation at STP after allowing the temperature to reach equilibrium. All samples were taken in triplicate and averaged to calculate experimental error and verify repeatability.

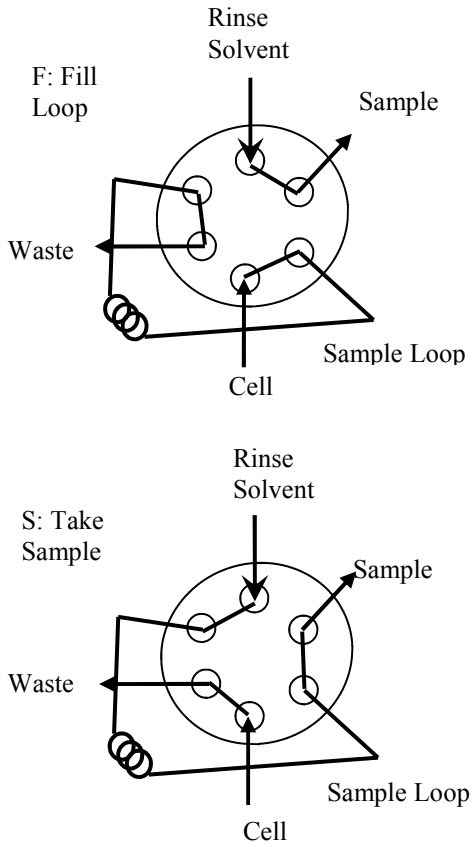


Figure 3 Sample loop modes and respective connections.

3 Results and Discussion

3.1 Solvent Screening and Cloud Points

It is necessary to determine quantitatively the ternary phase equilibria in the proposed organic-aqueous tunable solvent system, in order to design appropriately a chemical process. A range of common organic solvents were mixed with water and pressurized with propane at a fixed temperature to determine the range of pressures at which vapor-liquid-liquid equilibrium exists. The lower limit of the pressure range is given by the cloud point, or the first point at which the water-organic liquid phase splits into two distinct phases. The upper pressure limit is given by the point at which a third propane-rich liquid phase forms. The phase transitions for the propane tunable solvent systems are shown in Figure 4. Phase compositions are quantified using the direct sampling technique as outlined in the experimental section.

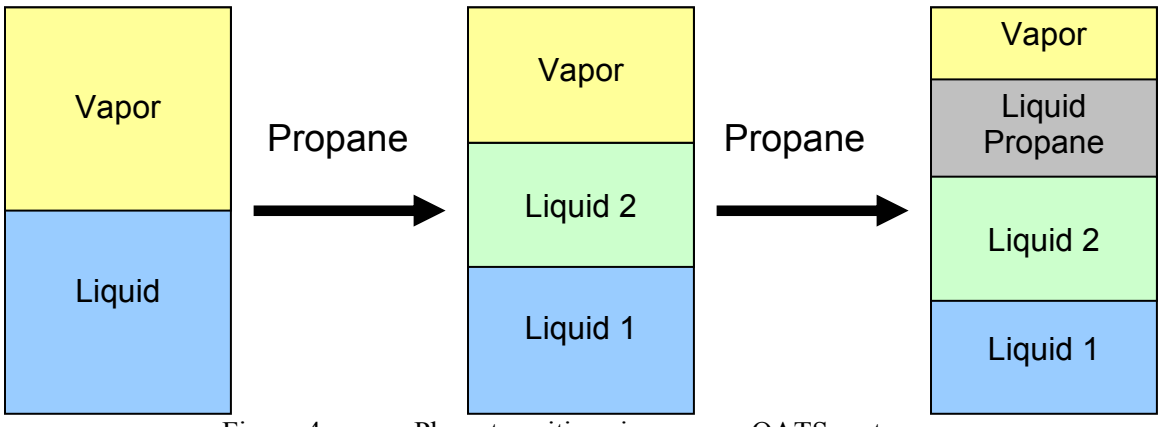


Figure 4 Phase transitions in propane OATS systems.

The following organic solvents were screened for feasibility because they are fully miscible with water at STP: acetone, acetonitrile, dimethylformamide, 1,4-dioxane, 1-

methyl-2-pyrrolidone, and tetrahydrofuran. Each system was comprised of water and organic solvent in the ratio of either 55/45 wt% or 33/67 wt% (water/organic) at either 303K or 313K. Table 1 shows the conditions where a 3 phase region is observed for each solvent system. Tetrahydrofuran readily separated from water; existing as a 3 phase system over a large operating pressure range. The water/tetrahydrofuran system was originally loaded with 55 wt% water, and separated at both 303K and 313K. Acetone existed as a 3 phase system over a smaller pressure range with an original water loading of 33 wt%, at 313K. The acetonitrile system observed a small 3 phase pressure range at 303K with an original water loading of 33 wt%. The remaining solvents, dimethylformamide, 1,4-dioxane, and 1-methyl-2-pyrrolidone, did not exist as a 3 phase region at either 303K or 313K.

Table 1 The observed conditions at which vapor-liquid-liquid equilibrium exists for water and an organic solvent under propane pressure.

Organic Phase	**Vapor-Liquid-Liquid Equilibrium Conditions**	
Acetone	9.7 bar to 18.3 bar 33 wt% Water(40°C)	
Acetonitrile	9.8 bar to 10.5 bar 33 wt% Water(30°C)	
Dimethylformamide	No organic-rich liquid phase observed	
1,4-Dioxane	No organic-rich liquid phase observed	
1-Methyl-2-Pyrrolidone	No organic-rich liquid phase observed	
Tetrahydrofuran	2.4 bar to 10.5 bar 55 wt% Water(30°C)	2.8 bar to 18.3 bar 55 wt% Water(40°C)

To cause a phase separation, the addition of propane must disrupt the interactions between the water and organic solvent. We speculate that the solvent polarity (E_t30), polarizability (π^*), boiling point, and hydrogen bonding (α, β) between the water and the organic solvent contribute to the miscibility or immiscibility for each three component system. These properties are displayed in Table 2 for each screened solvent. Additionally, the solubility of propane in the water/organic mixture must be sufficient to cause a co-solvent effect.

Table 2 Hydrogen bonding, polarizability, polarity, and boiling points of screened solvents.

Solvent	**Hydrogen bond donor (α)**	**Hydrogen bond acceptor (β)**	**Dipolarity/ polarizability (π^*)**	**E_t30**	**Boiling Point (°C)**
Acetone	0.08	0.43	0.71	42.2	56
Acetonitrile	0.19	0.40	0.75	45.6	82
Dimethylformamide	0.00	0.69	0.88	43.8	155
1,4-Dioxane	0.00	0.37	0.55	36.0	101
1-Methyl-2-Pyrrolidone	0.00	0.77	0.92	42.2	202
Tetrahydrofuran	0.00	0.55	0.58	37.4	65
Water	1.17	0.47	1.09	63.1	100

Water is a highly polar molecule that is a very strong hydrogen bond donor and good hydrogen bond acceptor. A solvent that is a strong hydrogen bond acceptor with a high polarity will interact strongly with water and be unlikely to phase separate under propane pressure. This explains why dimethylformamide and 1-methyl-2-pyrrolidone do not phase separate from water under pressurized conditions. Additionally, we speculate that

alcohols will not be a good choice of solvent due to their strong hydrogen bonding ability and high polarity; hence these solvents were not part of the screening process. The boiling point is another contributing factor to determine if a phase separation will occur because solvents with lower boiling points often exhibit weaker intramolecular forces, such as hydrogen bonding, London dispersion, and van der wals forces. Thus, solvents with lower boiling points and low polarities are more likely to phase separate from water with the addition of propane. The water/tetrahydrofuran and water/acetone systems show good phase separations and also have the lowest boiling points of the screened solvents with relatively low polarities and moderate hydrogen bonding capabilities.

The solubility of propane in the various water/organic systems must be sufficient to induce a co-solvent effect. The addition of propane causes varying amounts of volume expansion, sometimes greater than 3 times. As the volume of the solution increases, the concentration of water and organic decrease, reducing the strength of the interactions and contributing to the quality of the separation. This is evidenced by observing a phase separation after volume expansion in the water-acetone and water-tetrahydrofuran systems with propane pressure at 303K and/or 313K. In contrast, the water-acetonitrile, dimethylformamide, 1,4-dioxane, or 1-methyl-2-pyrrolidone systems experienced diminutive volume expansion resulting in a small or non-existent 3 phase pressure range.

Changing the mass ratio of the water to organic allows for further manipulation of the bond strength between the molecules present. There was no observed phase separation for the water-acetone and water-acetonitrile systems with a water concentration of 55

wt%, however decreasing the water to 33 wt% enabled these systems to become heterogeneous under propane pressure. Decreasing the amount of water in a system reduces the strength of the interactions between the water and organic. Additionally, hydrogen bonding strength decreases as the temperature of the solution increases. The water-acetone system (33/67 wt%) does not exist as a 3 phase system below the vapor pressure of propane (1.05 MPa) at 303K; however the desired 3 phase region exists at 313K.

Upon review of the screening results, the water/tetrahydrofuran and water/acetone systems were studied because they exhibit 3 phase regions over a wide pressure range. A representative range of pressures is chosen for each system, ensuring a sound understanding of the 3 phase region.

3.2 VLLE Water/Propane/Tetrahydrofuran

The cloud points for the water/propane/tetrahydrofuran system at 303K and 313K are 2.4 bar and 2.8 bar respectively. The pressure at which these cloud points are observed are the lowest reported in the literature. It is important to cause a phase separation at lower pressures to reduce operating costs of the resulting process. At STP, water and tetrahydrofuran are miscible at the concentrations studied; however this system experiences a lower critical solution temperature (LCST) at 345K [11]. The addition of propane reduces the LCST and we exploit this until vapor-liquid-liquid equilibrium is observed. Figure 5 shows the mass composition of each liquid phase in the water/propane/tetrahydrofuran system, originally loaded with 55 wt% water and 45 wt%

tetrahydrofuran, at 303K and pressures ranging from 0.37 to 0.92 MPa; an operating range of 0.55 MPa. Figure 6 shows the same ternary system at 313K and pressures ranging from 0.64 to 1.35 MPa; an operating range of 0.71 MPa. We observe no change in trend for the phase equilibria between 303K and 313K for the water/propane/tetrahydrofuran system. Table 3 and Table 4 represent the corresponding mass compositions for these systems.

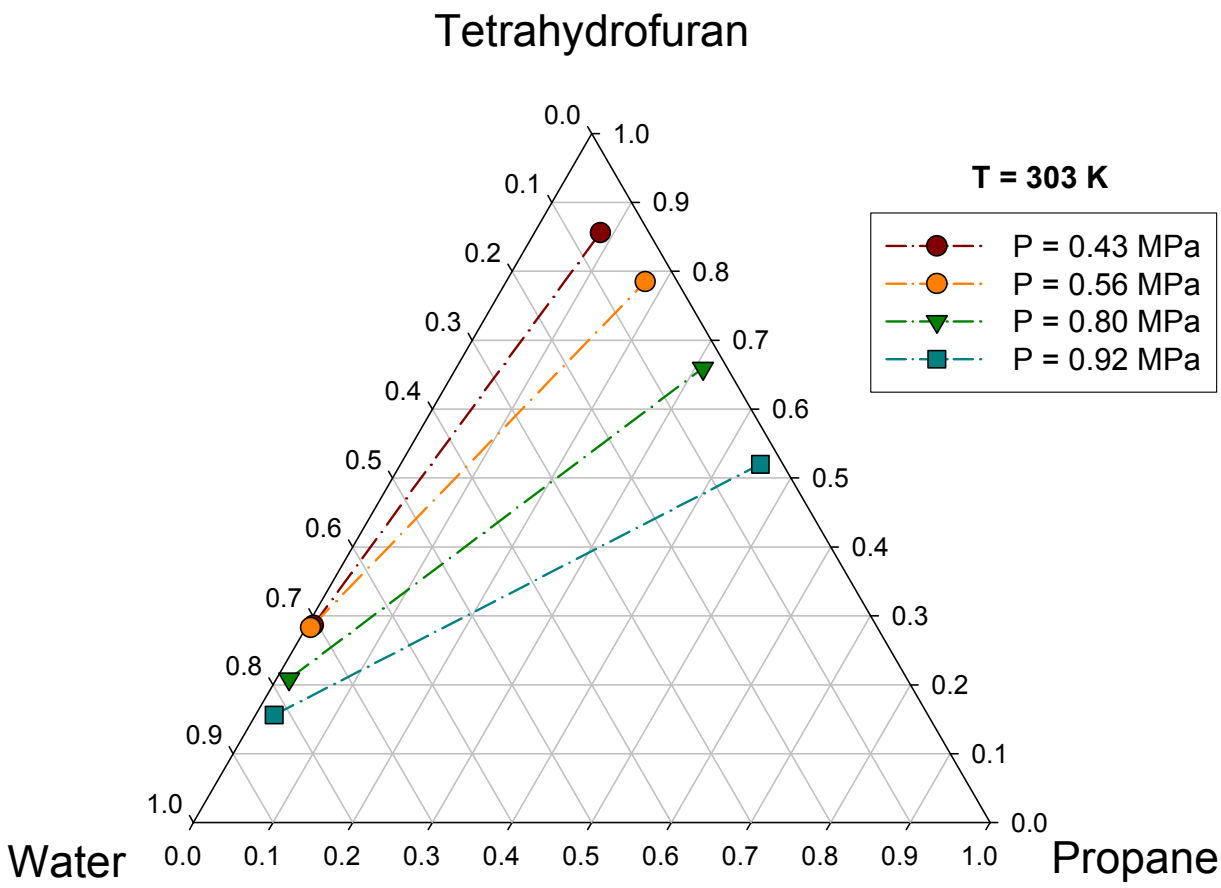


Figure 5 Ternary phase behavior of the water + propane + tetrahydrofuran system at T = 303 K.

Table 3 Ternary phase behavior of the water(1) + propane(2) + tetrahydrofuran(3) system at 303K.

P (Mpa)	Water-rich phase (L1)			Tetrahydrofuran-rich phase (L2)		
	x1	x2	x3	x1	x2	x3
0.43	0.706	0.008	0.286	0.061	0.083	0.856
0.56	0.711	0.006	0.283	0.040	0.175	0.785
0.80	0.776	0.016	0.208	0.031	0.310	0.659
0.92	0.820	0.024	0.156	0.028	0.452	0.520

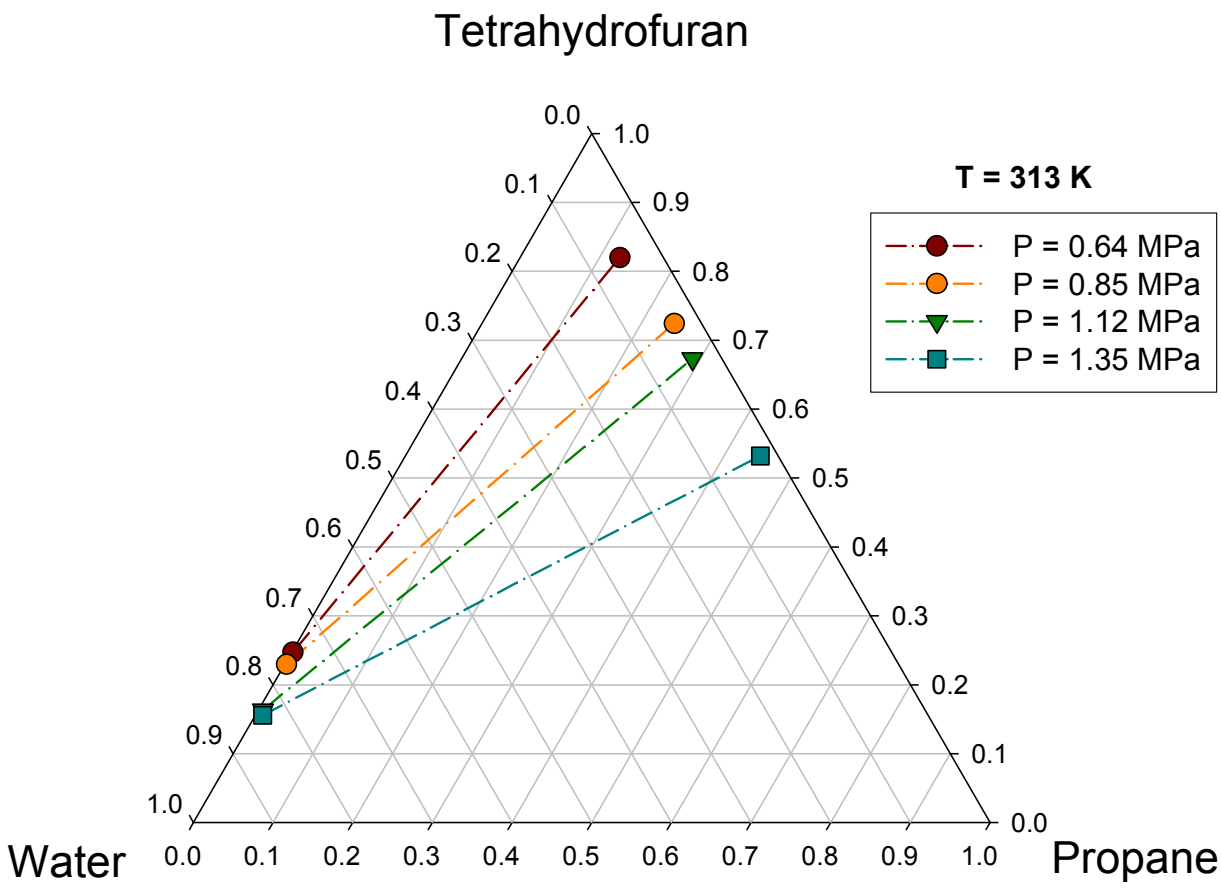


Figure 6 Ternary phase behavior of the water + propane + tetrahydrofuran system at T = 313 K.

Table 4 Ternary phase behavior of the water(1) + propane(2) + tetrahydrofuran(3) system at 313K.

P (Mpa)	Water-rich phase (L1)			Tetrahydrofuran-rich phase (L2)		
	x1	x2	x3	x1	x2	x3
0.64	0.752	0.001	0.247	0.055	0.126	0.819
0.85	0.769	0.002	0.229	0.034	0.242	0.724
1.12	0.831	0.006	0.163	0.037	0.290	0.673
1.35	0.836	0.009	0.155	0.022	0.446	0.532

3.3 VLLE Water/Propane/Acetone

In Figure 7 and Table 5 we show the water/propane/acetone system, originally loaded with 33 wt% water and 67 wt% acetone, at 313K and pressures ranging from 1.22 to 1.58 MPa; an operating range of 0.36 MPa. It was necessary to reduce the loaded water concentration to 33 wt% from 55 wt% because the acetone system did not enter a 3 phase region below the vapor pressure of pure propane. The 3 phase region for the acetone based system is much narrower than the examined tetrahydrofuran system. With both the acetone and tetrahydrofuran based systems, a 4 phase VLLLE region is observed within 0.1 MPa of the vapor pressure of pure propane at 303K and 313K. This suggests a mostly pure liquid propane phase forms in equilibrium with a mostly pure propane vapor phase, water-rich bottom liquid phase, and organic-rich middle liquid phase. This 4 phase VLLLE region was not studied in detail here.

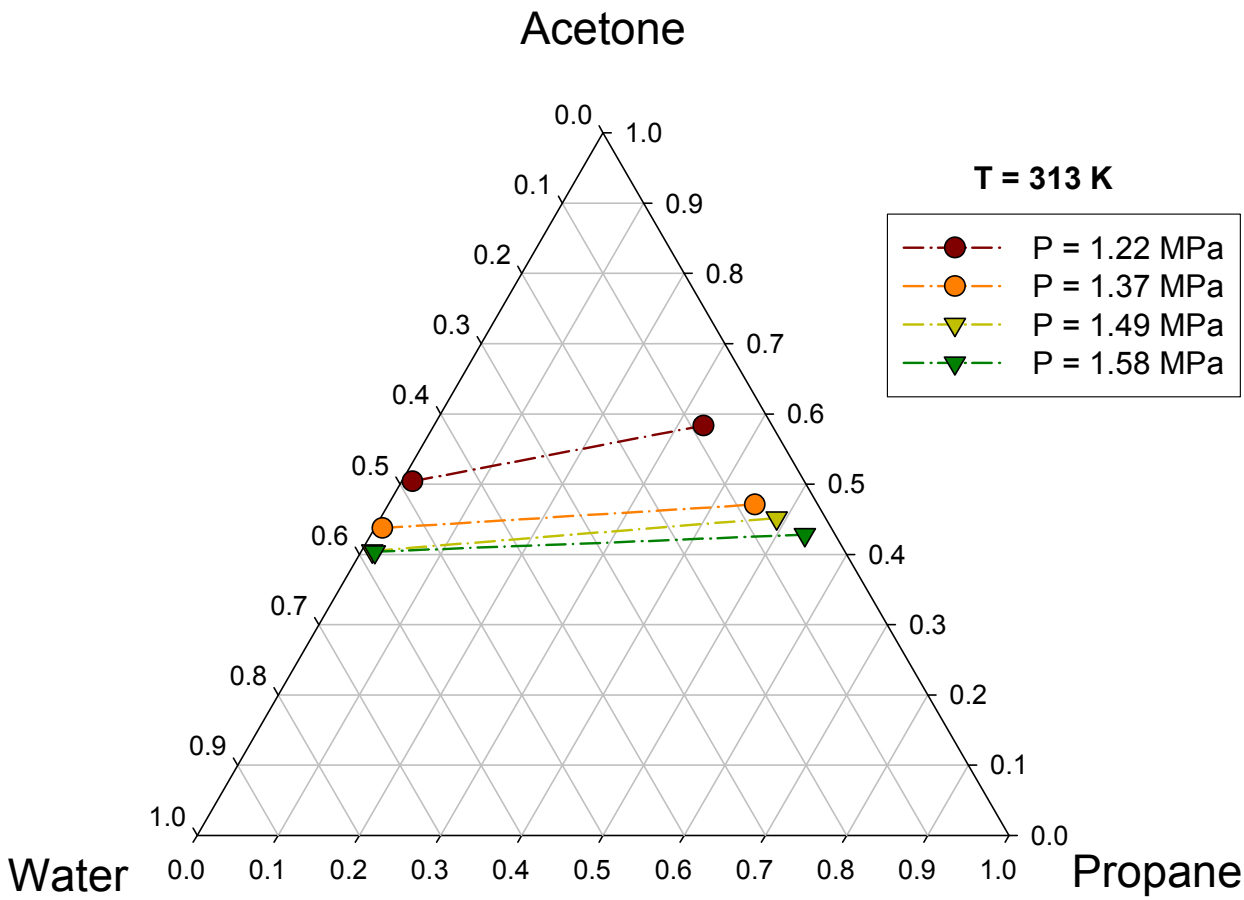


Figure 7 Ternary phase behavior of the water + propane + acetone system at T = 313 K.

Table 5 Ternary phase behavior of the water(1) + propane(2) + acetone(3) system at 313K.

P (Mpa)	Water-rich phase (L1)			Acetone-rich phase (L2)		
	x1	x2	x3	x1	x2	x3
1.22	0.483	0.013	0.504	0.085	0.332	0.583
1.37	0.553	0.010	0.437	0.078	0.452	0.470
1.49	0.582	0.013	0.405	0.060	0.488	0.452
1.58	0.579	0.017	0.404	0.038	0.534	0.428

3.4 Optimal Propane-OATS System

Since propane is a less reactive molecule than CO_2, acid is not formed *in-situ*. Catalytic reactions, such as enzymatic, base-catalyzed, and many carbon-carbon coupling reactions, sensitive to changes in pH, are made possible due to the elimination of carbonic acid from this organic-aqueous tunable solvent system. In addition, this system does not require a buffer to control pH. The addition of gas pressure causes the buffer to salt out rendering the buffer ineffective and introducing process difficulty associated with solids handling. The propane systems studied here eliminate acid formation and the need for solids handling while improving the quality of the phase separation when compared to CO_2 based systems.

Energy and cost requirements are important in determining the industrial feasibility of the described organic-aqueous tunable solvent system. In order to design a viable process, it is desirable to have a system pressure and temperature near atmospheric. Additionally, low product-phase contamination and minimal catalyst loss are essential. We compare the water concentrations in the organic-rich product phase as a measure of the quality of separation; since the catalyst is hydrophilic and the product is hydrophobic. Figure 8 shows the water content in the tetrahydrofuran-rich phase as a function of propane pressure. We speculate that the relation between the pressure and the amount of water in the organic phase is an exponential function and not linear. Initially, there are large percentage changes in the amount of co-solvent while being pressurized with propane. As the propane content in the organic phase increases; changes in the equilibrium diminish until either a limiting water content is reached or the propane-rich liquid phase forms. We

observe a water content in the tetrahydrofuran-rich phase under 3 wt% at pressures >0.8 MPa at 303K. In contrast, the water/CO_2/tetrahydrofuran system described by Lazzaroni et. al.[11] has a water content of 9 wt% at pressures >3.0 MPa at 298K. Our optimal system consists of water/propane/tetrahydrofuran originally loaded with 55 wt% water and 45 wt% tetrahydrofuran, at 303K.

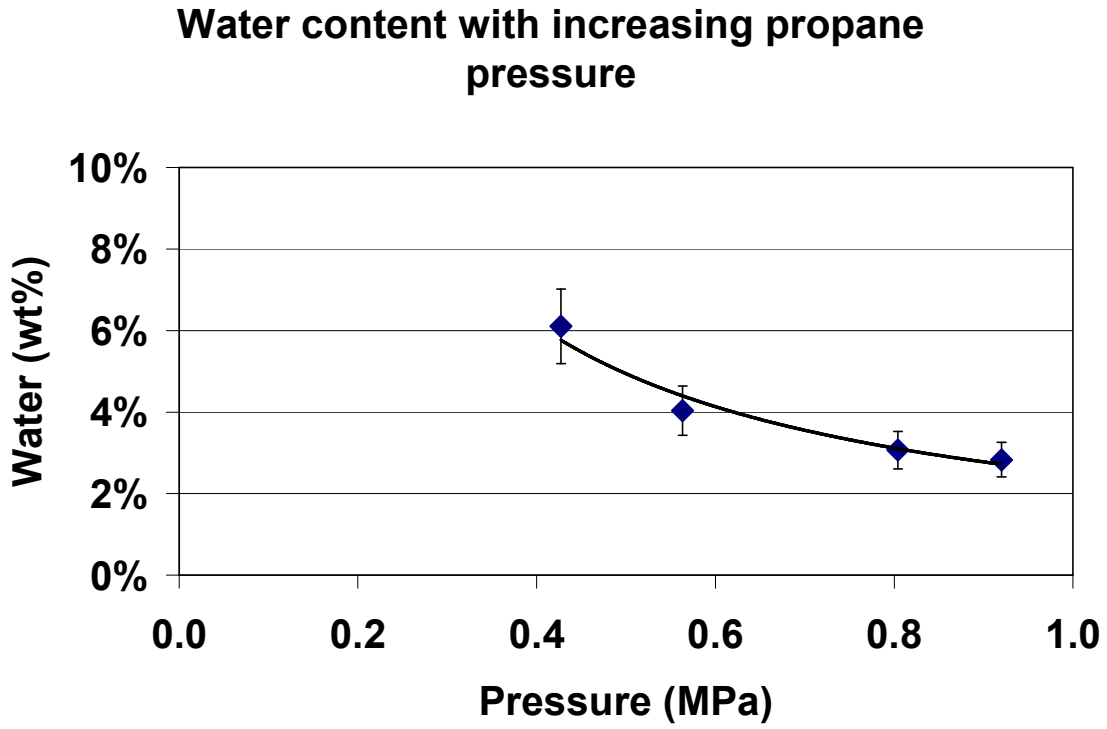


Figure 8 Water content in the tetrahydrofuran-rich phase with increasing propane pressure at T = 303K.

4 Conclusions

We present here the first use of propane as a miscibility switch for an organic-aqueous tunable solvent system. A study was conducted for the water/propane and either acetone, acetonitrile, dimethylformamide, 1,4-dioxane, 1-methyl-2-pyrrolidone, or tetrahydrofuran system. Phase diagrams are included for the water/propane/tetrahydrofuran system at 303K and 313K and the water/propane/acetone system at 313K. We observe a water content in the tetrahydrofuran-rich phase under 3 wt% at pressures >0.8 MPa at 303K; an improvement of 65% over the corresponding CO_2 based system[11]. Propane does not react with water or the organic solvents used here, and thus we have eliminated acid formation and created a more stable pH environment. Additionally, the elimination of a buffer simplifies the overall process by reducing the need for solids handling equipment. The studied propane-organic-aqueous systems improve further our tunable solvent systems; designed to couple the benefits of homogeneous catalysis with heterogeneous separations, while being environmentally sustainable.

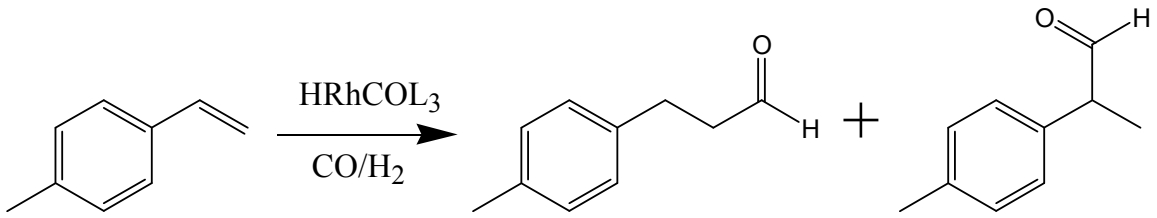
5 Recommendations

5.1 Hydroformylation of p-Methylstyrene

Performing example reactions, such as the hydroformylation of p-methylstyrene in the studied propane systems, will show the applicability of our tunable solvents for industrially relevant applications. The branched precursor for the pharmaceutically important drug Ibuprofen is produced via the hydroformylation of p-methylstyrene in the presence of syn-gas and a rhodium based catalyst. Ibuprofen is a pain killer with 30 million lbs produced annually[19]. A limitation of the industrial process to produce Ibuprofen is the need to use heterogeneously supported metal catalysts in order to recover the catalyst and run an economically viable process. The heterogeneous reaction of p-methylstyrene is mass transfer limited with a reaction time that is two orders of magnitude higher than the same reaction run homogeneously. Since the hydroformylation of p-methylstyrene is performed at 393K, we can dramatically decrease the energy requirement for this process by running this reaction homogeneously, while still being able to recover the catalyst. The proposed propane-based organic-aqueous tunable solvent system studied here presents an opportunity to use the advantages of a homogeneous reaction with an easy separation.

The hydroformylation of p-methylstyrene to form a linear and branched product is shown in Figure 9. The pharmaceutically relevant compound is the branched version of the product. Hallet et. al.[20] have studied various catalyst ligands for the hydroformylation of 1-octene, namely: triphenylphosphine (TPP), triphenylphosphine mono-sulfonated

sodium salt (TPPMS), and triphenylphosphine tris-sulfonated sodium salt (TPPTS). The optimal ligand based on high selectivities and turnover was TPPMS shown in Figure 10. We have obtained a branched to linear ratio of 20:1 with a turnover frequency of >300/hr in our optimal water/tetrahydrofuran system with $HRhCOL_3$ as a catalyst and TPPMS as a ligand.



p-methylstyrene Linear product Branched product

Figure 9 Hydroformylation of p-methylstyrene in the presence of syn-gas

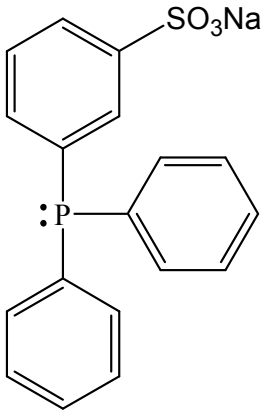


Figure 10 TPPMS (triphenylphosphine monosulfonate sodium salt) ligand

We can demonstrate the advantages of the propane tunable system by performing the homogeneous hydroformylation reaction followed by the heterogeneous separation. Trial recycles have been performed in the Jurguson cell after the hydroformylation reaction in a Parr reactor. Optimizing the water/organic ratio of the system as well as the reactant

and catalyst loading for both the reaction and separation should be performed. At least 3 catalyst recycles should be run in the Jerguson cell, with product yield measured and ideally no loss in catalyst activity. The catalyst recycles should also be performed in the CO_2 based systems as a control. We anticipate these results will show that the described system is a marked improvement over the CO_2 based tunable systems.

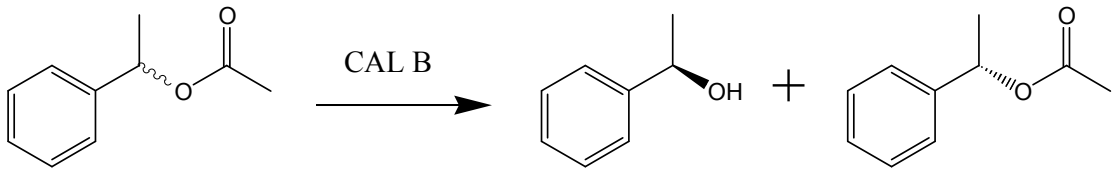
5.2 Chiral Resolution of rac-1-Phenylethyl Acetate

One of the advantages of the propane-organic-aqueous tunable solvent system described in this study is that carbonic acid is not formed *in-situ*. It is beneficial to show an enzymatic reaction as an example, in order to take advantage of the pH neutral environment. Enzymes are biological catalysts that can transform chemicals with very high chiral selectivities.

A chiral molecule is often found as a racemic mixture of enantiomers. These enantiomers are often difficult to separate because they have similar physical properties. Despite these similarities, the mirror image of a pharmaceutically desired chiral molecule may be toxic. For this reason, enantioselective synthesis is an important facet of pharmaceutical discovery.

Our group has previously explored the chiral resolution of a racemic mixture of 1-phenylethyl acetate (Figure 11) using the CO_2 based tunable solvent systems[21]. Hill et. al.[17] have shown that the solid buffer in the CO_2 based tunable systems, was not sufficient for controlling the pH of the system due to being salted out of solution upon the addition

of CO_2 pressure. Replacing the CO_2 with propane as a miscibility switch would further demonstrate the advantages of the propane tunable system.



rac-1-phenylethyl acetate (R)-1-phenylethanol (S)-1-phenylethyl acetate

Figure 11 Chiral resolution of *rac*-1-phenylethyl acetate using *Candida antarctica* lipase B (CAL B)

5.3 Additional Solvent Systems and Conditions

The water/propane/tetrahydrofuran and water/propane/acetone systems are studied here in detail. In order to expand the applicability of these propane-organic-aqueous tunable solvent systems we need to explore a wider range of organic solvents and the conditions at which the systems are studied; namely temperature and water/organic ratio. Table 1 details the conditions where a VLLE region occurs. The tetrahydrofuran/water binary system is fully miscible over a wide range of compositions. The water/propane/tetrahydrofuran system is studied at 55 wt% water at 303K and 313K, however the addition of 0.2 wt% of a hydrophobic reactant such as methylstyrene or phenylethyl acetate, causes a phase separation, even at STP. It is possible to run reactions with lower than 0.2 wt% reactant; however in most instances a higher reactant loading requires less solvents, produces more product, and has a lower energy requirement, making the process more sustainable. Reactions involving methylstyrene and phenyl ethyl acetate are described in sections 5.1 and 5.2.

To design a more versatile system we can explore the miscibility of the water/tetrahydrofuran system with a hydrophobic compound present at various water/organic ratios at STP. Additionally, we can revisit the water/acetone and water/acetonitrile systems with hydrophobic compounds present, such as methylstyrene or phenylethyl acetate. Should any of these solvent systems be fully miscible at STP with a reactant concentration of >2 wt%, detailed phase equilibria studies of the system with propane pressure should be conducted. The direct sampling technique should be used as the system would now be 4 components and can not be characterized via the synthetic method. The synthetic method would require volume measurements for 4 phases to measure 4 components, where we are interested in the 3 phase region.

Our tunable solvent systems can be further tuned by choosing organic solvents that are variations of tetrahydrofuran and acetone; namely by adding R groups to the base molecule. The purpose of the additional group would be to make the molecule more hydrophilic or hydrophobic by manipulating the hydrogen bonding ability and polarity of the organic solvent. The water/tetrahydrofuran system readily splits with the addition of the propane or reactants, thus we need to make the tetrahydrofuran more hydrophilic by adding an amine, hydroxyl, carboxyl, or methoxy group to the molecule, or by using a more hydrophilic ether. In contrast, the water/acetone system does not phase separate as readily with propane pressure as the water/tetrahydrofuran system, thus the acetone molecule must be made more hydrophobic. Methyl ethyl ketone has one additional carbon when compared with acetone, increasing the hydrophobicity of the molecule and

making it more likely to phase separate from the water with the addition of propane pressure.

As the volume of solvent will still be substantial, any modified organic solvent must be commercially available to be a viable substitute for tetrahydrofuran, acetone, or any other solvent studied here.By carefully choosing our solvent systems and operating conditions, including temperature and water/organic ratio; the current water/propane/tetrahydrofuran and water/propane/acetone systems can be improved to suit individual reactions and their respective separations.

References

1 J.M. DeSimone. Practical approaches to green solvents. *Science*, **2002**, 297, 799-803.

2 R.A. Sheldon. Green solvents for sustainable organic synthesis: state of the art. *Green Chem.*, **2005**, 7, 267-278

3 E.J. Beckman. Supercritical and near-critical CO_2 in green chemical synthesis and processing. *J. Supercrit. Fluids*, **2004**, 28, 121-191.

4 P.G. Jessop, B. Subramaniam. Gas-expanded liquids. *Chem. Rev.*, **2007**, 39, 362-380.

5 A. Kruse, E. Dinjus. Hot compressed water as reaction medium and reactant: Properties and synthesis reactions. *J. Supercrit. Fluids*, **2007**, 39, 362-380.

6 D.J. Heldebrant, H.N. Witt, S.M. Walsh, T. Ellis, J. Rauscher, P.G. Jessop. Liquid polymers as solvents for catalytic reductions. *Green Chem.*, **2006**, 8, 807-815.

7 T. Welton. Room-temperature ionic liquids. Solvents for synthesis and catalysis. *Chem. Rev.*, **1999**, 99, 2071-2084

8 K.N. West, J.P. Hallett, R.S. Jones, D. Bush, C.L. Liotta, C.A. Eckert. CO_2-induced miscibility of fluorous and organic solvents for recycling homogeneous catalysts. *Ind. Eng. Chem.* Res., **2004**, 43, 4827-4832.

9 L.C. Draucker, J.P. Hallett, D. Bush, C.A. Eckert. Vapor-liquid-liquid equilibria of perfluorohexane + CO_2 + methanol, + toluene, + acetone at 313K. *Fluid Phase Equilib.*, **2006**, 241, 20-24.

10 M.E. Donaldson, L. Draucker, V. Blasucci, C.L. Liotta, C.A. Eckert. Liquid-liquid equilibria of polyethylene glycol (PEG) 400 and CO_2 with common organic solvents. *Fluid Phase Equilib.*, **2009**, 277, 81-86.

11 M.J. Lazzaroni, D. Bush, R. Jones, J.P. Hallett, C.L. Liotta, C.A. Eckert. High-pressure phase equilibria of some carbon dioxide–organic–water systems. *Fluid Phase Equilib.*, **2004**, 224, 143-154.

12 R.R. Weikel, J.P. Hallett, C.L. Liotta, C.A. Eckert. Self-neutralizing in situ acid catalysts from CO_2. *Top. Catal.*, **2006**, 37, 75-80.

13 J.M Broering, E.M. Hill, J.P. Hallett, C.L. Liotta, C.A. Eckert, A. Bommarius. Biocatalytic reaction and recycling by using CO_2-induced organic-aqueous tunable solvents. *Angew. Chem.*, **2006**, 45, 4670-4673.

14 J.C. Elgin, J.J. Weinstock. Phase equilibrium at elevated pressures in ternary systems of ethylene and water with organic liquids. Salting Out with a Supercritical Gas. *J. Chem. Eng. Data*, **1959**, 4, 3-12.

15 T. Adrian, M. Wendland, H. Hasse, G. Maurer. High-pressure multiphase behaviour of ternary systems carbon dioxide–water–polar solvent: review and modeling with the Peng–Robinson equation of state. *J. Supercrit. Fluids*, **1998**, 12, 185-221.

16 J. Freitag, M.T. Sanz Diez, D. Tuma, T.V. Ulanova, G. Maurer. High-pressure multiphase behavior of the ternary systems (ethene + water + 1-propanol) and (ethene + water + 2-propanol) Part I: Experimental investigation. *J. Supercrit. Fluids*, **2004**, 32, 1-13.

17 E.M. Hill. Benign tunable solvents for improved processing of pharmaceutically relevant products and catalysts. Dissertation, Georgia Institute of Technology, **August 2007**.

18 M.J. Lazzaroni. Optimizing solvent selection for separation and reaction. Dissertation, Georgia Institute of Technology, **July 2004**.

19 M. Doble, A. Kumar, A.K. Kruthiventi. Green Chemistry and Processes. Academic Press, **2007.**

20 J.P. Hallett, J.W. Ford, R.S. Jones, P. Pollet, C.A. Thomas, C.L. Liotta, C.A. Eckert. Hydroformylation catalyst recycle with gas-expanded liquids. *Ind. Eng. Chem.* Res., **2008**, 47, 2585-2589.

21 E.M. Hill, J.M. Broering, J.P. Hallett, A. Bommarius, C.L. Liotta, C.A. Eckert. Coupling chiral homogeneous biocatalytic reactions with benign heterogeneous separation. *Green Chem.*, **2007**, 9, 888-893.